INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

*I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the Application and Complete Specification filed in connection with Application for Patent No.**24/Del/2002** dated 15th **January 2002**.*

Witness my hand this 31st day of January 2003.

(H.C. BAKSHI)
Joint Controller of Patents & Designs

24/DEL/01
7/3/01

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5 (2), 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **" PROCESS FOR THE PREPARATION OF A STABLE PHARMACEUTICAL COMPOSITION COMPRISING ACE INHIBITOR(S)"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. DEEPAK BAHL

b. RAVI KOCHHAR

c. PUNEET SHARMA

d. VISHNUBHOTLA NAGAPRASAD

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Group Leader – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, DEEPAK BAHL, RAVI KOCHHAR, PUNEET SHARMA, VISHNUBHOTLA NAGAPRASAD of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. (DEEPAK BAHL)

b. (RAVI KOCHHAR)

c. (PUNEET SHARMA)

d. (VISHNUBHOTLA NAGAPRASAD)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **678118** dated **12.11.2001** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **15th** day of **January, 2002.**

For Ranbaxy Laboratories Limited

(S K PATAWARI)
Company Secretary

0024-DEL-2

FORM 2

15 JAN 2002

The Patents Act, 1970

(39 of 1970)

COMPLETE SPECIFICATION

(See Section 10)

PROCESS FOR THE PREPARATION OF A STABLE PHARMACEUTICAL COMPOSITION COMPRISING ACE INHIBITOR(S)

DUPLICATE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for the preparation of a stable pharmaceutical composition comprising ace inhibitor(s), which are susceptible to degradation.

Certain Angiotensin Converting Enzyme (ACE) inhibitors, which are useful as antihypertensives, are susceptible to certain types of degradation. ACE inhibitor such as ramipril, quinapril, enalapril, spirapril, lisinopril, benazepril and structurally related drugs undergo cyclization due to internal nucleophilic attack to form substituted diketopiperazines. These drugs also degrade via hydrolysis (of the side-chain ester group) and oxidation to form products having unwanted coloration.

It has been found that a significant cause of such degradations is the mechanical stress associated with the manufacturing process of pharmaceutical composition such as compression. The stability of pharmaceutical compositions containing ACE inhibitors is also influenced by the choice of tabletting auxiliaries.

In view of the usefulness of ACE inhibitors in treating hypertension, a number of research endeavors have been directed towards overcoming the inherent instability problem associated with ACE inhibitor-containing compositions.

For example U.S. Pat. No. 4,743,450 discloses a stable pharmaceutical composition containing an alkali or alkaline earth metal carbonate to minimize cyclization and discoloration and also suitable amount of a saccharide to inhibit hydrolysis of ACE inhibitors.

U.S. Pat. No. 4,830,853 discloses a pharmaceutical composition containing an ACE inhibitor stabilized against oxidation and discoloration using ascorbic acid and/or sodium ascorbate and at least one lubricant and/or excipient or mixtures thereof which do not interfere with the function of stabilizer.

U.S. Pat. No. 4,793,998 discloses a pharmaceutical composition containing ascorbic acid alone or in combination with organic acids such as fumaric, maleic and citric acid as cyclization and/or hydrolysis inhibitors with at least one lubricant and/or excipient.

The PCT application published as WO 99/62560 discloses ACE inhibitor compositions stabilized by the presence of magnesium oxide.

The European patent EP 468929 discloses use of acid donors such as amino acid hydrochlorides and Lewis acid chlorides as the stabilizing component.

The U.S. Pat. Nos. 5,151,433 and 5,442,008 disclose a protective coating of the pure active ingredient such as ramipril and structurally related drugs with polymeric film-formers before compression to counter act the mechanical inactivation.

The said patent also discloses the use of a buffer such as sodium dihydrogen phosphate dihydrate, trisodium citrate dihydrate, sodium carbonate, sodium hydrogen carbonate and tris-(hydroxymethyl)aminomethane to ensure weakly acidic to weakly alkaline range of pH (such a pH is said to be set up in the formulation under the action of atmospheric humidity) for stabilizing pharmaceutical compositions of ramipril and structurally related drugs.

The stabilizing effect produced by mixture with buffer may be combined with protective polymeric coating of the particles of active ingredient.

In the light of the foregoing it is clear that either addition of a stabilizer or a polymeric coat on the active ingredient is necessary to stabilize the pharmaceutical composition of ACE inhibitors, which are susceptible to degradation.

The addition of an acid or buffer or alkali earth metal carbonate as stabilizer may produce unwanted pharmacological effects. Coating the active ingredient is quite cumbersome and low yielding, moreover it requires specialized equipment.

The applicants of the present invention have discovered a novel process, which makes the use of the above unnecessary. In the present invention active ingredient i.e. ACE inhibitor, which is susceptible to degradation is applied as a coat to the core, preferably to a compressed core, thereby avoiding the degradation (such as cyclization to diketopiperazine) induced by the mechanical stress, which builds up during the compression. Such an arrangement also avoids the direct contact of the tabletting auxiliaries with the ace inhibitor thereby preventing degradation by any incompatible tablet auxiliaries.

The present invention therefore provides greater flexibility in the choice of tabletting auxiliaries. Moreover, as no additive is needed to stabilize the composition, any untoward pharmacological effect, which could occur with the addition of such additives, is nullified. The process can be easily scaled up using the conventional tabletting and coating equipment.

Therefore, the object of the present invention is to provide a process for the preparation of a stable pharmaceutical composition for oral administration of the ACE inhibitor comprising a core coated with a layer of ACE inhibitor(s).

The core of the present invention is preferably a compressed core, which could be inert or may contain a drug other than the ACE inhibitor susceptible to degradation such as hydrochlorothiazide, piretanide; and dihydropyridines such as felodipine, nitrendipine, nifedipine and lacidipine etc.

However, alternatively the core may be a starch or sugar sphere such as non pareil sugar seeds.

The compressed core may comprise diluent and other formulating agents such as binder, disintegrant, lubricant and glidant. The diluent may be selected from any pharmaceutically acceptable, non-toxic diluent such as lactose, dextrose, sucrose, maltose, microcrystalline cellulose, starch, calcium hydrogen phosphate and mannitol.

Binders may be selected from the group consisting of starch, sugars, gums, low molecular weight hydroxypropyl methylcellulose and hydroxypropylcellulose.

Disintegrant may be selected from the group consisting of croscarmellose sodium, crospovidone, sodium starch glycolate, bentonite, sodium alginate, and hydroxypropylmethylcellulose.

Lubricants may be selected from the group consisting of talc, magnesium stearate, calcium stearate, polyethylene glycol, hydrogenated vegetable oils, stearic acid, sodium stearyl fumarate and sodium benzoate. Glidants may be selected from Colloidal silicon dioxide (aerosil) or talc.

The ACE inhibitor layer comprises ACE inhibitor(s), which are susceptible to degradation such as ramipril, spirapril, lisinopril, enalapril, quinapril, benazepril and other structurally related drugs. The ACE inhibitor is preferably micronized, and suspended/dispersed in a solvent to which film forming polymer(s) is added. The film forming polymer may be selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, ethylcellulose, cellulose acetate, polyvinylpyrrolidone, gelatin, LustreClear™ (combination of microcrystalline cellulose and carrageenan) and a combination of polyvinylalcohol and polyvinylacetate. The amount of the film forming polymer(s) is normally kept to a minimum in order to limit the tablet/pellet/beadlet size and the manufacturing effort. On the other hand it should be sufficient to effectively coat the drug on to the core. The drug to polymer ratio may range from 1:10 to 10:1.

The polymer that is used for binding properties also protects the ACE inhibitor from aerial oxidation and degradation by atmospheric humidity such as hydrolysis.

The ACE inhibitor layer may optionally contain plasticizers such as polyethylene glycol, triethylcitrate, triacetin, dibutyl phthalate, diethyl phthalate, dimethyl phthalate, benzyl benzoate, butyl and glycol esters of fatty acids, refined mineral oils, oleic acid, stearic acid, cetyl alcohol, stearyl alcohol, castor oil, corn oil and camphor.

Besides plasticizers it may also contain pigments, colorants, antifoaming agents, waxes, monoglycerides, emulsifiers, surfactants and other additives.

Solvents that can be used for drug coating include water, isopropyl alcohol, ethanol, acetone, methylene chloride or mixtures thereof.

A seal coat may optionally separate the core and the ace inhibitor layer to completely seal the tabletting auxiliaries to come in contact with the ACE inhibitor.

Similarly, an outer coat may optionally be given on the ACE inhibitor layer to improve the aesthetic appeal of the tablet and to protect it from the atmospheric humidity.

The seal coat and outer coat may have the same composition as the ACE inhibitor layer except the drug.

The process of the present invention may be carried out in the following manner.

The compressed core is prepared by the techniques known in the art such as direct compression, wet granulation and dry granulation.

The ACE inhibitor coating dispersion is prepared by dispersing the active ingredient(s) in the solvent with stirring. Film forming polymer(s), plasticizer and other additives are added to the active ingredient dispersion with stirring. The cores are charged into a coating pan and warmed with air to an outlet-air temperature of about 30°C-45°C. The ACE inhibitor coating dispersion is sprayed onto the cores and upon completion, the drug coated tablets is dried with dry air.

Seal coat and outer coat dispersion may be prepared and applied in the similar manner as the ACE inhibitor layer, if required.

The coated tablets after air-drying are packed into containers impervious to water vapor, e.g. blister packs (alu-alu; PVDC, PE, PVC-alu).

The present process may also be applied to the Non pareil seeds or beadlets, which may then be filled in hard gelatin or starch capsules.

Using the process parameters of the present invention, a convenient, reproducible stable pharmaceutical composition of the ACE inhibitors may be obtained. The present invention is further illustrative by, but is by no-means limited to, the following examples.

Example-1

INGREDIENT	WEIGHT(mg)
Core	
Mannitol	44.50
Microcrystalline cellulose	43.50
Pregelatinized starch	10.0
Sodium Stearyl Fumarate USNF	2.0
Tablet Weight	**100.00**
Seal Coat	2
Hydroxypropylmethylcellulose(67%)	
Hydroxypropylcellulose(6.7%)	
Polyethylene glycol(12%)	
Titanium dioxide(10%)	
Talc(6.3%)	
Purified water (q.s)	
Target Weight	**102.00**
Drug layer	
Ramipril	2.5
Film forming Polymer	2.5
Hydroxypropylmethylcellulose(67%)	
Hydroxypropylcellulose(6.7%)	
Polyethylene glycol(12%)	
Titanium dioxide(10%)	
Talc(6.3%)	
Purified water (q.s)	
Target Weight	**107.00**
Outer Coat	2.0
Hydroxypropylmethylcellulose(67%)	
Hydroxypropylcellulose(6.7%)	
Polyethylene glycol(12%)	
Titanium dioxide(10%)	
Talc(6.3%)	
Purified water (q.s)	
Total Weight	**109.00**

Preparation of tablet core

In non shear blender, microcrystalline cellulose, Pregelatinized starch & Mannitol are mixed and to this mixture Sodium Stearyl Fumarate is added and mixed. The mixture is then compressed to tablets of 100 mg each.

Preparation of the seal coating solution

Hydroxypropylmethylcellulose, Hydroxypropylcellulose, Polyethylene glycol, Titanium dioxide, Talc are dispersed in water with stirring and the suspension homogenized.

Preparation of the drug coating suspension

Ramipril is dispersed in water with stirring and to it Hydroxypropylmethylcellulose, Hydroxypropylcellulose, Polyethylene glycol, Titanium dioxide, Talc are added. The suspension is homogenized.

Preparation of the outer coating solution

Outer-coating solution is prepared similar to the seal coat solution.

Coating of the tablet core

Tablet cores were placed in the coating pan (Hi-Coater) and heated with warm air to an air outlet temperature of about 30°C-45°C. The seal coating solution was sprayed on the cores. Upon completion the heating was discontinued but the air supply was maintained for about 10 minutes in order to dry the tablets.

The coated cores were sprayed with the drug coating solution and air dried maintaining the process parameters as for the seal coat.

Similarly, the outer coating solution was then sprayed on the drug coated cores. The tablets were air dried and extracted from the apparatus and packed in suitable pack.

Example-2

INGREDIENT	WEIGHT(MG)
Core	
Hydrochlorothiazide	25.0
Mannitol	40.0
Dibasic Calcium Phosphate (Anhydrous)	97.855
Starch	19.60
Pregelatinized Starch	4.4
Ferric Oxide (Red)	0.165
Ferric Oxide (Yellow)	0.33
Purified Water	q.s
Pregelatinized Starch	11.00
Magnesium Stearate	1.65
Tablet Weight	**200.00**
Seal Coat	4.00
Hydroxypropylmethylcellulose(67%)	
Hydroxypropylcellulose(6.7%)	
Polyethylene glycol(12%)	
Titanium dioxide(10%)	
Talc(6.3%)	
Purified water (q.s)	
Target Weight	**204.00**
Drug layer	
Ramipril	5.0
Film forming Polymer	5.0
Hydroxypropylmethylcellulose(67%)	
Hydroxypropylcellulose(6.7%)	
Polyethylene glycol(12%)	
Titanium dioxide(10%)	
Talc(6.3%)	
Purified water (q.s)	
Target Weight	**214.00**
Outer Coat	4.00
Hydroxypropylmethylcellulose(67%)	
Hydroxypropylcellulose(6.7%)	
Polyethylene glycol(12%)	
Titanium dioxide(10%)	
Talc(6.3%)	
Purified water (q.s)	
Total Weight	**218.00**

Example-3

INGREDIENT	WEIGHT(MG)
Core	
Mannitol	44.50
Microcrystalline cellulose	43.50
Pregelatinized starch	10.0
Sodium Stearyl Fumarate USNF	2.0
Tablet Weight	**100.00**
Seal Coat	2
Hydroxypropylmethylcellulose	
Purified water (q.s)	
Target Weight	**102.00**
Drug layer	
Ramipril	2.5
Hydroxypropylmethylcellulose	2.5
Purified water (q.s)	q.s
Target Weight	**107.00**
Outer Coat	
Hydroxypropylmethylcellulose	2.0
Purified water (q.s)	
Total Weight	**109.00**

Examples 2-3 are prepared as per the process given in Example-1.

A stability comparison with conventional tablets having Ramipril in the core with or without buffer and marketed ramipril tablets (Delix) of Aventis is shown in the table given below.

TABLE 1: Stability comparison of 2.5-mg ramipril tablets prepared by different composition/techniques

Degradation product	Condition	Ramipril tablets			
		Conventional compressed tablet	Compressed tablet with tris-(hydroxymethyl)amino methane buffer	Tablets prepared as per example 1	Delix marketed ramipril tablets of Aventis
Diketopiperazine	Initial	1.91	0.048	0.262	-
	60°C/2 weeks	18.48	4.61	4.42	5.91
Total Related substances	Initial	1.95	0.072	0.47	-
	60°C/2 weeks	19.22	7.26	4.59	-

The data clearly show that the tablets prepared by the process of present invention provides the most stable tablets.

CLAIMS:

1. A process for the preparation of a stable pharmaceutical composition for oral administration of ACE inhibitor(s) comprising a core coated with a layer of ACE inhibitor(s).

2. The process according to claim 1 wherein the ACE inhibitor is selected from the group consisting of Ramipril, Quinapril, enalapril, spirapril, lisinopril, benazepril and structurally related compounds.

3. The process according to claim 1 wherein the ACE inhibitor coating comprises ACE inhibitor and film forming polymer.

4. The process according to claim 3 wherein the film forming polymer(s) is selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, ethylcellulose, cellulose acetate, polyvinylpyrrolidone, gelatin, LustreClear™ (combination of microcrystalline cellulose and carrageenan) and a combination of polyvinylalcohol and polyvinylacetate.

5. The process according to claim 3 wherein the ACE inhibitor coating further has a plasticizer, pigments, colorants, antifoam agents, wax, monoglycerides, emulsifiers, surfactants and other additives.

6. The process according to claim 5 wherein the plasticizer is selected from the group consisting of polyethylene glycol, triethylcitrate, triacetin, dibutyl phthalate, diethyl phthalate, dimethyl phthalate, benzyl benzoate, butyl and glycol esters of fatty acids, refined mineral oils, oleic acid, stearic acid, cetyl alcohol, stearyl alcohol, castor oil, corn oil and camphor.

7. The process according to claim 3 wherein the ACE inhibitor coating suspension is made with solvents selected from the group consisting of water, isopropyl alcohol, ethanol, acetone, methylene chloride or mixtures thereof.

8. The process according to claim 1 wherein the core is a compressed tablet.

9. The process according to claim 1 wherein the core has a drug other than the ACE inhibitor, susceptible to degradation.

10. The process according to claim 9 wherein the drug is selected from the group consisting of hydrochlorothiazide, piretanide; and dihydropyridines such as felodipine, nitrendipine, nifedipine and lacidipine.

11. The process according to claim 1 wherein a seal coat separates the core and the ace inhibitor layer.

12. The process according to claim 1 wherein the ACE inhibitor layer is further surrounded with an outer coat.

13. A process for the preparation of a stable pharmaceutical composition for oral administration of the ACE inhibitor substantially as described and illustrated by the examples herein.

Dated this **15TH** day of **January, 2002.**

For Ranbaxy Laboratories Limited

(S K Patawari)
Company Secretary